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08/327,522	10/21/94	LOCKHART	D 16528X86

EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/327,522	Applicant(s) Lockhart et al
	Examiner Jeffrey Fredman	Group Art Unit 1807

☒ Responsive to communication(s) filed on *Feb 21, 1996* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part III DETAILED ACTION

Drawings

1. Applicant's request that drawing corrections be held in abeyance until notice of allowable subject matter is accepted.

Specification

2. Correction of the specification is noted.

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to target nucleic acids without repeats. See M.P.E.P. §§ 706.03(n) and 706.03(z). While the breadth of these claims includes target nucleic acid of any length and known or unknown sequence the specification lacks guidance on a variety of information necessary to determine unknown sequences or long sequences. Specifically, no algorithms by which the data would be analyzed are presented. The absence of information regarding data analysis is critical, since it does not appear to be a simple problem to analyze varying intensity signals from a variety of oligonucleotides, and correctly identify the correct

sequence even with the addition of enzymatic discrimination. Further, unknown sequences may pose a variety of problems for the technique and software. Unknown sequences with long repeats, greater than the length of the interpreting oligos will be unreadable by this technique. The use of enzymatic discrimination adds another set of sequences which will be uninterpretable, which are sequences which are of equal length to the oligonucleotide but differ in a single base pair. Such sequences would previously have been read as ambiguous, but now may allow for correct identification of a first sequence at the expense of an inability to identify or incorrectly identify a second sequence. The amount of direction or guidance presented in the specification is minimal given that no information regarding modes of data analysis, duplicate sequences which differ by a single base pair, or repeat sequences is present. There are no working examples of sequencing initially unknown sequences, or sequences containing duplications, nor sequences of sufficient complexity to truly require computer assisted analysis. There is some prior art (Drmanac et al U.S. Patent 5,202,231) which discusses sequencing by hybridization and the problem of repeat sequences but does not give a solution which will allow for sequencing of any repeats. Although the level of skill in the art of nucleic acid hybridization is high (the Ph.D. degree with laboratory experience), there is no predictability for which sequences would be capable of being sequenced in this

method, nor is there any predictability for which mode of data analysis is capable of discriminating the exceedingly complex pattern that would result from a sequence of ordinary genomic length. A gene of only 2000 nucleotides would consist of 1992 8-mers, some of which might represent duplicates, and would represent approximately 3% of all 8-mer sequences, or 48% of all 6-mer sequences. If the gene was the size of the **B** -globin locus, which exceeds 60,000 basepairs in size and would have more than 60,000 6- or 8-mers, it could potentially utilize every possible 6- or 8-mer sequence. It is unclear how such a gene would be analyzed by the method disclosed, particularly using the arrays of claims 5-7 which are sufficiently small to be overwhelmed by relatively short sequences. The quantity of experimentation that would be necessary to determine methods by which any sequence of any size could be sequenced versus the non-repeating sequences is substantial. Accordingly, undue experimentation is required to make and use the invention as broadly claimed.

Response to Amendment - 112, first paragraph

4. Applicant's arguments filed February 21, 1996 have been fully considered but they are not deemed to be persuasive.

Applicant's arguments with regard to the explicit length limitation are correct and this point is withdrawn in the rejection in favor of the points regarding repeating sequences and new problems introduced by the method.

Applicant argues that teachings from WO 92/10588 serve to enable this specification. First, the incorporation of essential material by reference to a foreign application is improper. If Applicant believes that this material, essential to the practice of the invention will enable the invention, Applicant should have incorporated this information into the original specification prior to filing. This does not represent an invitation for such incorporation nor for prolonged after final prosecution. Second, art submitted by applicant supports the argument that substantial unaddressed problems exist in sequencing by hybridization as stated on page 3072 by Broude et al, (Proc. Natl. Acad. Sci. (1994) 91:3072-3076) including the ambiguity issue discussed above, anomalous behavior by oligonucleotides and secondary structure problems in DNA among other issues.

Finally, Applicant did not address one element of the rejection. The rejection noted that use of a nuclease to remove non-hybridizing sequences would, in some instances, degrade sequence performance. The following specific example demonstrates this point. For a target sequence ACGTAGGT which is to be read using different 4-mer oligos, ACCT and ACGT, the discrimination would obliterate the target. Incorrectly annealing target where the ACGT oligo hybridizes to the AGGT sequence would cause removal of this sequence. Similarly, annealing of the ACCT oligo to the ACGT sequence would cause removal of the second sequence. This problem would prevent

efficient sequencing of closely related repeat sequences, alleles and other sequences where the sequence contains multiple, almost identical nucleotide sequences within the entire region to be sequenced.

Claim Rejections - 35 USC § 112

5. The rejection of claims 1-18 under 35 U.S.C. § 112, second paragraph, are withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

7. Claims 1-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor et al (WO 92/10588) in view of Sambrook et al (Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, p. 5.80, 7.58-7.78)

Fodor teaches a method of sequencing comprising the steps: a) combining a_i) an oligonucleotide array composed of 8- to 15-mers (page 26) and up to 10^6 oligonucleotides (page 11), a_{ii}) a target nucleic acid to form hybrid complexes, c) detecting remaining complexes bound to oligonucleotides (page 4, also pages 34-36).

Fodor does not teach step b) adding a nuclease to digest hybrid complexes which are not perfectly complementary nor the use of specific nucleases.

Maniatis teaches methods of S1 mapping and ribonuclease protection assays in which S1 nuclease or RNAse A are used to remove unbound and imperfectly complementary hybrid complexes (pages 7.58-7.78). Maniatis also teaches that Mung Bean nuclease is functionally equivalent to S1 nuclease (page 5.80).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the sequencing method of Fodor with the use of nuclease to distinguish perfectly complementary hybrid complexes from imperfectly complementary complexes as taught by Maniatis since Maniatis states that in S1 mapping "DNA that has not formed duplexes is hydrolyzed with nuclease S1, whereas DNA that has

hybridized to RNA is protected from digestion (page 7.58)". Maniatis further states in regard to ribonuclease protection assays "The sensitivity of this method is therefore approximately 20-fold greater than that attained with double-stranded DNA probes . . . Furthermore, the digestion of RNA:RNA hybrids with RNAase appears to suffer fewer artifacts than digestion of RNA:DNA hybrids with nuclease S1. For these reasons and because of the relative ease with which radiolabeled RNA probes can be synthesized, it is not surprising that RNAase digestion of RNA:RNA hybrids has become a standard method to quantitate mRNA molecules (page 7.71, paragraph 3)". An ordinary practitioner would have been motivated to combine the method of Fodor with the nuclease methods of Maniatis for the explicitly stated benefits of sensitivity, reduction of artifacts, and ease of use in the removal of imperfectly hybridizing molecules for better detection of perfectly hybridizing molecules.

8. Claims 17 and 18 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor in view of Keith et al (U.S. Patent 5,093,245).

Fodor teaches a method of sequencing comprising the steps: a) combining a_i) an oligonucleotide array composed of 8- to 15-mers (page 26) and up to 10^6 oligonucleotides (page 11), a_{ii}) a target nucleic acid to form hybrid complexes, c) detecting remaining complexes bound to oligonucleotides (page 4, also pages 34-36).

Fodor does not teach the ligation of labeled oligonucleotides for detection of DNA, nor does Fodor teach the use of T4 DNA ligase in that detection.

Keith teaches the ligation of labeled oligonucleotides with T4 DNA ligase for the detection of DNA (column 2, lines 29-42 and columns 7 and 8).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the sequencing method of Fodor with the ligation of labeled oligonucleotides method of Keith since Keith states "It is evident from the above results that a simple effective process for labeling or modifying termini of double-stranded DNA is provided. Smaller amounts of the labeling moiety are required, wail oligomerization of the sample is substantially prevented. Labeling can occur in the same reaction vessel in which restriction or specific fragmentation is accomplished. Thus a homogenous product is obtained which provides for accurate sizing, detection and ease of further manipulation (column 9, lines 3-11)". An ordinary practitioner would have been motivated to combine the methods of Fodor and Keith for the expressly stated and expected benefits of simplicity, accuracy of detection, and ability to use small amounts of the label.

9. Claims 17 and 18 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor in view of Broude et al (Proc. Natl. Acad. Sci. (April 1994) 91:3072-3076).

Fodor teaches a method of sequencing comprising the steps: a)combining a_i) an oligonucleotide array composed of 8- to 15-mers (page 26) and up to 10^6 oligonucleotides (page 11), a_{ii})a target nucleic acid to form hybrid complexes, c) detecting remaining complexes bound to oligonucleotides (page 4, also pages 34-36).

Fodor does not teach the ligation of labeled oligonucleotides for detection of DNA, nor does Fodor teach the use of T4 DNA ligase in that detection.

Broude teaches the ligation of labeled oligonucleotides with T4 DNA ligase for the detection of DNA in a sequencing by hybridization method (page 3072, column 2 and abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the sequencing method of Fodor with the ligation of labeled oligonucleotides method of Broude since Broude states "Enzymatic steps can further improve the discrimination against mismatches. Ligation at high salt concentration and elevated temperature proceeds efficiently with perfectly matched duplexes but not mismatches. Similar ligation conditions have been used for the detection of single base mutations. Another important advantage of using a ligation step in SBH is that there is comparatively little effect of base composition on match-mismatch discrimination which is a serious problem seen in ordinary SBH (page 3076, column 1)". An ordinary practitioner would have been

motivated to combine the methods of Fodor and Broude for the expressly stated and expected benefits of improved specificity due to discrimination against mismatches.

Response to Amendment - 103 rejection

10. Applicant's arguments filed January 21, 1996 have been fully considered but they are not deemed to be persuasive.

Applicant makes two arguments with regard to the 103 rejections of Fodor in view of Sambrook and Fodor in view of Keith. In each case applicant argues a lack of suggestion to combine and argues the use of hindsight reasoning.

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CCPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA) 1969. In this case, the invention of Fodor in view of Maniatis is composed of two elements. The first element is the method of

sequencing by hybridization which is clearly taught by Fodor. The second, novel element is the use of an enzyme such as a nuclease to discriminate between mismatches by enzymatic digestion of such mismatches. Fodor explicitly points out the problems posed by mismatches, stating "Mismatched hybridization may a problem with the polynucleotide sequencing applications (page 24, lines 23-24)". The art recognizes a number of methods to deal with mismatches in hybridization. One method is to adjust hybridization temperatures or buffers. A second method, exemplified in the Maniatis reference, is to use enzymes such as RNAse to digest mismatched nucleic acids. Applicant's argument which focuses on the specific elements of the Maniatis method is misplaced. Applicant focuses on the element that Maniatis does not explicitly state that the method would be useful in sequencing methods. Applicant is correct in this assertion, however the ordinary practitioner would recognize that multiple methods are available to remedy the deficiency identified by Fodor. One such method would be RNAse or S1 nuclease discrimination of mismatches as taught by Maniatis. The ordinary practitioner would recognize this combination as functional to minimize the Fodor's specific problem of mismatches.

Applicant also argues that there is no suggestion to combine Fodor and Keith. This argument is also not persuasive since it fails to account for suggestions which would be motivate the ordinary practitioner. The invention rendered obvious by Fodor

in view of Keith is to utilize a ligase and additional oligonucleotide as a label in a sequencing by hybridization assay. Fodor explicitly identifies a number of potential labels useful in the sequencing by hybridization method including "radioisotopes, chemiluminescent compounds, labeled binding proteins, heavy metal atoms, spectroscopic markers, magnetic labels and linked enzymes (page 73, lines 3-6)". Keith presents a new labeling method which an ordinary practitioner would recognize as functionally equivalent to the other labeling moieties. This functional equivalence as well as the benefits expressly stated by Keith would motivate an ordinary practitioner to utilize the method of Keith generically with any other assay which requires detection.

In response to Applicant's second argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. *In re McLaughlin*, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971).

11. No claims are allowable over the prior art.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

The rejection is made final since the new ground of rejection was necessitated by applicant's submission of a reference not previously considered.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by fascimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-7939. Please note that the faxing of such papers must conform with the

Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman, Ph.D.

March 25, 1996

STEPHANIE W. ZITOMER
PRIMARY EXAMINER
GROUP 1800